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| EXAMINER | |
|---|---|
| FETTEROLF, BRANDON J | |

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| 1642 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 09/771,312 | **Applicant(s)** JAKOBOVITS ET AL. | |
|---|---|---|---|
| | **Examiner** Brandon J. Fetterolf, PhD | **Art Unit** 1642 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 07 August 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *12,14,15 and 39*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached document.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

***Response to the Amendment***

The Amendment filed on 08/07/2007 in response to the previous Final Office Action (10/20/2004) is acknowledged and has been entered.

Claims 12, 14-15 and 39 are currently pending and under consideration.

**Rejections Maintained:**

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 12, 14-15 and 39 are/remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 12, 14-15 and 39 are directed to an isolated recombinant protein comprising the amino acid sequence of SEQ ID NO: 2, wherein the recombinant protein is encoded by a nucleotide sequence of SEQ ID NO: 1. However, neither the specification nor any art of record teaches what the amino acid sequence of SEQ ID NO: 2 is, how it functions, or a specific and well-established utility as claimed. The specification asserts (page 15, lines 28-29 and page 16, lines 1-18) that the polypeptides of the invention can be utilized to generate antibodies for use in detecting 84P2A9 overexpression or the metastasis of prostate cells and/or cells of other cancers expressing the gene. Thus, it presumed that there is a correlation between the overexpression of the polypeptide and a particular disease state. Furthermore, the specification teaches (page 18, lines 15-17) that the proteins of the invention may also be used in the forensic analysis of tissues of unknown origin.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other

compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where *specific* benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

Although the specification discloses a nexus between the polynucleotide expression and a disease state (see for example page 75, Example 3), the specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polypeptide. If a molecule such as the polypeptide of SEQ ID NO: 2 is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. Many polypeptides may be expressed in normal tissues, as well as diseased tissues. Therefore, one needs to know, e.g., that the claimed polypeptide is present only in cancer tissue to the exclusion of normal tissue. Thus, in the absence of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from various expression profiles in both normal and diseased tissue only serves as the basis for further research on the observation itself.

Furthermore, those of skill in the art recognize that over expression of a particular nucleic acid specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. There are many steps in the pathway leading from DNA to protein, and all of them can, in principle, be regulated. For example, Alberts *et al.* (Molecular Biology of the Cell, 3rd edition, 1994, page 465, *of record*) illustrate post-transcriptional regulation of ferritin wherein the translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation.

Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferin receptor polypeptide is translated. Lewin, B. also teaches (Genes VI, Oxford University Press, Inc., NY, Chapter 29, 1997, *of record*) that a major control point for genes exists during the initiation of transcription by the interaction of the RNA polymerase with its promoter. Concurring with Alberts *et al.*, Lewin further acknowledges downstream control of gene expression since translation of mRNA in the cytoplasm is also a point of control. Also, with regards to tumor associated antigens, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401, *of record*) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Furthermore, Mallampalli *et al.* (Biochem. J. Vol. 318, 1996, pages 333-341, *of record*) teach that the glucocorticoid, betamethasone, increased mRNA expression of cholinephosphate cytidylyltransferase (CT) as determined by RT-PCR and Southern analysis, but did not alter the levels of the CT enzyme as assayed by Western blotting (abstract, and page 339, 2nd column, 2nd paragraph). Finally, Lewin acknowledges that control of gene expression can occur at multiple stages and that production of RNA *cannot inevitably* be equated with production of protein. Thus, the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, absent evidence of the polypeptide expression including the correlation to a particular diseased state, for example present and/or absent as compared to control, one of skill in the art would not be able to predictably use the invention in a way that constitutes a specific and substantial utility and as disclosed do not meet the requirements of 35 U.S.C. §101 as being useful.

Claims 12, 14-15 and 39 also are/remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In response to this rejection, Applicants assert that the Examiner does not get to choose which asserted utility is relied upon for patentability, the choice falls solely to Applicants. In particular, Applicants assert that while the claimed protein has other credible, substantial, and specific uses, the claimed protein, for the purpose of prosecution, is useful as a therapeutic target for antibodies directed against such cancer cells. Thus, Applicants assert that the Examiners discussion

of issues regarding overexpression and issues regarding other possible utilities, e.g., diagnosis, for the claimed subject matter is completely irrelevant to the issue of whether the pending claims satisfy the utility requirement because Applicants need only assert a single credible assertion of specific utility of the claimed invention to satisfy the utility requirement. Applicants further assert that the Examiners assertions that the claimed protein might be expressed in normal prostate cells as well as cancerous ones is in error because all that need be shown for the claimed protein to be useful as required by the statue is that the protein be expressed by cancerous prostate cells since once a diagnosis of prostate cancer is made (by methods that were readily available at the time the application was filed) elimination of cancerous prostate cells becomes the paramount interest. Similarly, Applicants assert that the Examiners concern that antibodies directed against the claimed protein could not distinguish between normal prostate cells and cancerous prostate cells is misplaced since the loss of normal prostate cells while eliminating cancerous prostate cells is inconsequential from the point of evaluating utility because the point of prostate cancer therapy is to eliminate prostate cancer cells. Thus, Applicants assert all that needs to be shown to satisfy the utility requirement is that it is more than likely than not that cancerous prostate cells will be killed using antibodies generated from the claimed protein, and therefore, it would make no difference at all to one of ordinary skill in the art if normal prostate cells are killed while cancerous prostate cells are also killed. In addition, Applicants assert that the declaration filed by Dr. Morrison which provides evidence that the claimed protein is expressed by cancerous prostate cells is more than adequate to support Applicants' asserted utility. In particular, Applicants assert that the evidence by Dr. Morrison provides a nexus between mRNA and detectable protein expression; and questions pertaining to the overexpression of the claimed protein in normal cells are not relevant to the issue of utility because Applicants have demonstrated that the claimed protein is detected on cancerous prostate cells. Applicants further point to a recent Board of Patent Appeals and Interferences decision which reversed an examiners utility rejection with contours similar to those in this case. In Ex part Ashkenazi, the Board agreed with applicants that the Examiner failed to show a sufficient basis to challenge the asserted utility. For example, the Board found that the Examiner had overstated the conclusions of a reference which allegedly undermined the nexus between c-fos and angiogenesis, much like the Examiner in the present case has overstated the alleged lack of nexus between mRNA levels and protein levels.

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner acknowledges and agrees with Applicants assertions that Applicants need only assert a single credible assertion of specific utility of the claimed invention to satisfy the utility requirement. However, in contrast to Applicants assertions that the arguments that Examiners discussion of issues regarding overexpression and issues regarding other possible utilities, e.g., diagnosis, for the claimed subject matter is completely irrelevant to the issue of whether the pending claims satisfy the utility requirement, as noted previously, the Examiner does not see a difference in being a target for treating cancerous prostate cancer cells and being a diagnostic for prostate cancer cells because there still needs to be some type of expression pattern that would allow the claimed polypeptide to be useful as a "target" on prostate cancer cells vs. normal prostate cells and/or any other normal tissue. Thus, while the Examiner agrees with Applicants assertions that once a diagnosis of prostate cancer is made (by methods that were readily available at the time the application was filed) elimination of cancerous prostate cells becomes the paramount interest. However, the Examiner recognizes that the treatment of cancer using monoclonal antibodies is not as trivial as Applicants assert. As noted previously, Weiner (Seminars Oncology, Vol. 26, No.4, 1999, pages 41-50) provided an overview of monoclonal antibody of therapy including some promising activity, however major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets, insufficient target specificity, and induction of HAMA (page 43). Regarding Applicants assertion with respect to a nexus between mRNA and the protein in prostate cancer cells, the Examiner acknowledges and agrees with Applicants that the Dr. Morrison declaration provides evidence that the polypeptide is expressed on prostate cancer cells via antibody detection. However, as noted previously, there is no evidence to suggest that the claimed protein is underexpressed or over expressed in normal prostate cancer cells lines. Lastly, regarding Applicants submission of the BPAI decision in Ex part Ashkenazi, the Examiner acknowledges and agrees with the Boards decision in that case. However, the Examiner recognizes that the fact patterns involved in this case are different from those in Ex part Ashkenazi. For example, in Ex pat Ashkenazi the claims where drawn to an antibody which binds a protein asserted by Applicants to be associated with angiogenesis, e.g., a biological process involved in cancer cells. In contrast, the instant claims

encompass a protein which Applicants found to expressed on prostate cancer cells. However, there is no expression pattern in normal prostate cells and the protein does not appear to be associated with any particular biological function related to prostate cancer. As such the fact patterns are different.

Therefore, NO claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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